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Fatalities after taking ibogaine in addiction treatment could be related to sudden cardiac death caused by autonomic dysfunction

U. Maas *, S. Strubelt

Scientific African Society, Röhrchenstr. 63, 58452 Witten, Germany

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Summary Ibogaine is the most important alkaloid of the Central African Iboga-shrub. It is the central drug in Gabonian initiation ceremonies in which it is used to cause a near-death experience. In Western countries it is used in private clinics to treat addiction. However, in the United States and most European countries it is classified as an illegal drug because at least eight persons have died after having taken Ibogaine. These fatalities occurred in most cases several days after ingestion or following the intake of very small doses. There is no conclusive explanation at the present time for these deaths.

We hypothesize, that these deaths may be a result of cardiac arrhythmias, caused by a dysregulation of the autonomic nervous system.

Ibogaine affects the autonomic nervous system by influencing several neurotransmitter-systems and the fastigial nucleus. The cerebellar nucleus responds to small doses with a stimulation of the sympathetic system, leading to a fight or flight reaction. High doses, however, lead to a vagal dominance: a "feigned death".

The risk of cardiac arrhythmias is increased in situations of sympathetic stimulation or coincidence of a high parasympathetic tonus and a left-sided sympathetic stimulation. This could occur under influence of small doses of ibogaine and also at times of exhaustion with a high vagal tonus, when sudden fear reactions could cause a critical left-sided sympathetic stimulation. Gabonian healers prevent these risks by isolating their patients from normal life and by inducing a trance-state with right-hemispheric and vagal dominance for several days.

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Introduction

In the United States in the 1960s, drug addicts discovered by chance, that following the intake of a single dose of ibogaine, extracted from the Gabonian iboga-shrub, they experienced no craving

and felt no need for drugs any more. Since then, self-help groups in several countries demand the legalization and utilization of ibogaine in public health systems [1]. Private clinics started using ibogaine in addiction treatment and could prove positive effects in a clinical study [2]. Nevertheless, ibogaine remains to be classified as an illegal drug in most Western countries. One of the reasons is the fact that at least eight persons in Europe and

* Corresponding author.

E-mail address: umaas@scientific-african.org (U. Maas).

in the United States to date have died following the intake of the drug. The fatalities occurred under remarkable circumstances: some of the fatalities being several days after ibogaine consumption or after the oral intake of relative small doses of the drug. Four persons had taken less than half of the dose recommended for drug therapy of 20–30 mg/kg of body weight ([1,3] and personal inquiries).

To date, there is no conclusive explanation for the fatalities. Several authors hold the destruction of cerebellar Purkinje-cells responsible, a process that could be demonstrated in rats after the intake of high doses of ibogaine (100 mg/kg injected intraperitoneally) [1,4,5]. Cerebellar neurotoxicity, however, should cause long-term problems concerning movement coordination rather than sudden death [1]. Other authors suspect that the deceased had taken opioids concurrent with ibogaine. There is evidence suggesting that the interaction of opioids and ibogaine potentiates opioid toxicity [1,5].

At least two persons died who had taken ibogaine for spiritual reasons and were presumably not addicted. And also in Gabon, where people to be initiated are usually young healthy men and women, the risk of death is well known and part of the initiation-myth [6–8]. To protect the person to be initiated, Gabonian healers perform a long, complicated ritual that lasts between several days and many weeks. In most Western cases, the people were alone at the moment of an unexpected death. In Gabon, these individuals would have been watched and accompanied by the healing community.

Autonomic dysfunction as a risk for sudden unexplained death

To date, medical monitoring of patients treated with ibogaine showed, as far as we are informed, no benefit. People died unexpectedly after the monitoring phase, and we have no information about any case of successful life-saving measures. We suggest therefore, that ibogaine-related fatalities should be classified as sudden and unexplained death syndrome (SUDS). The term, SUDS, means that no specific medical reason can be identified, a psychological cause is often suspected [9]. This corresponds to the African theory that attributes deaths during initiation rituals to spiritual causes.

A considerable number of investigations have found an imbalance of the autonomic nervous system with a well-known increase of risk of SUDS in patients suffering from schizophrenia [10–12] and epilepsy [13–15]. Autonomic dysfunction as a con-

sequence of an immature cerebellum is also made responsible for the sudden infant death syndrome [16–19]. Imbalance of the autonomic nervous system is also frequent and could explain increased mortality in patients with depression, post-traumatic stress disorder, anxiety and stress [20–23]. Animal studies could prove that psychological stress can cause autonomic dysfunction and deaths in captured wild animals [24]. Patients with pre-existing cardiovascular diseases or permanent autonomic dysfunction (for example, in cases of epilepsy) may be particularly sensitive to stress-effects [25].

Ibogaine-related fatalities: Sudden cardiac deaths?

Effects of ibogaine on the autonomic nervous system are well known. Small doses help participants of Gabonian night-long ceremonies to remain awake. Tablets with 8 mg content of ibogaine were sold in the 1960s in Europe as a stimulant [26]. There is evidence of several contradictory mechanisms. Ibogaine increases parasympathetic as well as sympathetic effects by inhibition of cholinesterase. At the same time it weakens autonomic functions as an antagonist of nicotine receptors and agonist of sigma2 receptors [1,5]. In both cases, it blocks calcium-channels and by this way reduces the synaptic transmission of acetylcholine [27]. On the other hand, ibogaine is a muscarinic receptor agonist and increases by this way parasympathetic functions.

In addition, ibogaine has an indirect influence on the autonomic nervous system by its stimulating effect on Purkinje-cells and on the fastigial nucleus [28]. This cerebellar nucleus affects the autonomic nervous system, especially in situations of shock and life threatening danger. At the same time, it induces measures of protection against cerebral ischemia. These effects have been proven to be maintained for weeks [29], so it could be assumed, that also changes of the autonomic nervous system after cerebellar stimulation last for some time.

Interestingly, the influences of the fastigial nucleus on the autonomic system are varying. Dependent on the situation, stimulating or inhibiting effects on sympathetic and parasympathetic functions have been observed [30–33]. This makes sense, since in a life-threatening situation there are two options for mammals: to be active (fight/flight reaction) or to freeze (feigned death). The first reaction consists of a sympathetic stimulation and parasympathetic inhibition to enable fight or flight. If this is impossible, a reaction of

“feigned-death” follows that helps to deceive the enemy and also to protect vital functions. A parasympathetic dominance leads to a bradycardia and a reduction of respiratory and metabolic rate and inhibition of movements [34,35]. The two phases were shown in fright-reactions of infants [36] and rats [37]. Vingerhoets [38] could also observe tachycardia in dental patients, which was replaced by a freezing reaction and bradycardia during the treatment.

Sudden cardiac death as a result of autonomic dysfunction

Abundant evidence suggests that SUDS, as a result of autonomic dysfunction, is caused by ventricular fibrillation, which is provoked by a sympathetic overreaction or asymmetric stimulation of the autonomic nervous system [39,40]. There are several mechanisms, that can possibly cause lethal arrhythmias:

1. Sympathetic overactivity increases cardiac inotropy and chronotrophy leading to a lengthening of the QT-interval and may cause electrical inhomogeneity of the myocardium with ventricular extrasystoles because of early after-potentials. Dispersion of refractoriness facilitates the genesis of re-entrant circuits in the presence of an initiating premature beat [39, p. 369].
2. Sympathetic stimulation causes an increased vascular tonus that adds to the increased cardiac activity and may cause ischemia in myocardial cells particularly in cases of a pre-existing cardiac disease [39, p. 370].
3. Another risk factor for stress-triggered heart failure is an imbalanced activity in right and left cardiac sympathetic nerves, namely a left-sided sympathetic overstimulation [40–42]. Lateralized cortical and subcortical activation during the central processing of stress tasks is channelled ipsilaterally and results in lateralized imbalance of neuronal input to the heart. These inputs influence the heart in different ways. The sinus node, which governs heart rate, is influenced predominantly by the right hemispheric sympathetic nerve [42]. But additionally and partly independently, the ventricular myocardium is governed by left-hemispheric sympathetic nerves [43,44]. If left-hemispheric sympathetic stimulation becomes stronger than right-hemispheric stimulation, autonomous ventricular frequency may pass the one of the sinus node, leading to ventricular extrasystoles. Situations of exhaustion, when a high vagal tonus

inhibits right hemispheric stimulation and lowers sinus node frequency, imply an increased risk for this kind of cardiac arrhythmias. Sudden left hemispheric, stress-triggered, sympathetic stimulation may even provoke cardiac death [40].

The described mechanisms are based on sympathetic influences and can thus be triggered by stress. They lower the ventricular fibrillation threshold and may cause sudden death by “torsade de pointes”. These theoretical considerations could be proven in animals studies by sympathetic stimulation [40,41] or stimulation of the fastigial nucleus [45]. Critchley et al. [42] found the arrhythmogenic effect of left-hemispheric triggered stress in humans. Abundant evidence exists for the increased mortality of persons with high sympathetic tonus [46–48].

In at least two fatalities following ibogaine intake, a pre-existence of cardiac problems could be proven ([1,3] and personal inquiries). We therefore hypothesize, that ibogaine related fatalities are SUDS, caused by heart failure, which is triggered by autonomic dysregulation under simultaneous stress. We presume, that the risk in drug-addiction treatment or initiation rites after application of higher doses of ibogaine (more than 10 mg/kg of body weight) is reduced during the peak of ibogaine-effects. The “vision” is caused by a strong parasympathetic stimulation. Bradycardia, reduction of respiratory rate and movements can be observed in the ritual context [6, p. 95,7]. We presume, that this state of parasympathetic dominance and right-hemispheric trance protects the cardiovascular system. Cardiac problems should be expected after the intake of small doses (less than 10 mg/kg of body weight) and in the period before and after the peak-level with lower ibogaine-effects. We presume, that especially the state of exhaustion after the peak-level includes the risk that a high parasympathetic tonus hits to a strong and left-hemispheric sympathetic stimulation in a situation of a sudden stress.

Gabonian healers try to avoid sudden excitement by keeping the person to be initiated isolated from the normal life and in an extraordinary inner and outer space maintaining the hypnotic state [6, p. 39]. The trance state activates the right cortical hemisphere [49,50] and the ritual music induces a slow cerebral theta-rhythm of 5–6 Hz, causing a feeling of rest and calmness [51,52]. Through this, sudden sympathetic reactions, which may endanger the heart, are prevented.

Sebastiani et al. [53] consider trance states and hypnosis to be an effective prevention against car-

diac arrhythmias, because fright reactions are dampened. Hypnosis inhibits the arousal system of the amygdala [50]. If this system fails, cardiac arrhythmias as reaction on frightening stimuli are blocked [54].

Conclusions

We claim, that fatalities following the intake of ibogaine should be considered to be related to the drug, even if they occur several days after the peak-level of ibogaine. In Gabon, a phase of at least three days is considered as a critical period.

We hypothesize, that fatalities after ibogaine intake are sudden cardiac deaths as a result of a dysregulation of the autonomic nervous system in combination with psychological stress. This dysregulation is caused by direct interactions of ibogaine with several neurotransmitter systems and by its stimulation of the fastigial nucleus. The latter may have long-term effects.

The main risks for a sudden cardiac failure include a sympathetic overstimulation or a sudden left-hemispheric sympathetic reaction in a phase of high parasympathetic tonus. This could occur in the time after the peak level of the drug.

Gabonian healers protect their clients by induction of a right-hemispheric hypnotic trance-state which lasts for days and prevents sudden fear-reactions. Their statement, that fatalities during the initiation ceremony have "spiritual" causes fits with our hypothesis. It remains to be investigated, if other parts of the complex ritual such as nutrition or movements, may have a protective effect.

To prove our hypothesis it would be useful to investigate the long-term effects of stimulation of the fastigial nucleus and the autonomic nervous system.

Further field research in Gabon could provide more information about traditional medical knowledge, particularly about situations and periods of increased risk for sudden fatality. Gabonian healers have a vast field of experience in a country with more than 100,000 initiated individuals.

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